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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,788	09/22/2000	Frank P. Wolter	MAIWAM2.001CP1	2349

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,788	WOLTER ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 13-17* is/are pending in the application.

4a) Of the above claim(s) *13-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6 and 13-17 are still at issue and are present for examination.

Applicant's election with traverse of Group I, Claims 1-6 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that coexamination of the process claims of group I and the product claims of groups II-IV makes it possible for the first time to synthesize the products as claimed in groups II-IV and that the products of groups II-IV has never been described or produced by any other process in the prior art. Applicants also argue that the products were unknown until their production by the novel process of group I and hence their relationship between group I and groups II-IV justifies examination of these groups together. Examiner respectfully disagrees. First of all the elected claims of group I constitute a method and groups II-IV constitute products. The two groups are related as method of making and products made and constitutes distinct inventions. Furthermore, contrary to applicants argument that these products were never synthesized or never known until their invention is highly misplaced. References provided by applicants themselves, indicate that these compounds were known in the prior art and also synthesized in other ways (see for example page 11 of the article by Kates M, Handbook of Lipid Research wherein monoglycosyldiacylglycerol and diglucosyldiacylglycerol has been purified to homogeneity on a TLC plate). Furthermore, irrespective of the fact that these compounds were known or unknown it is proper to restrict between the products and the method of making the products. Applicants also argue that it would not be a serious burden to the Examiner to search groups I and II-IV together because of their classification. This is not found persuasive because while the searches for these groups

may appear to overlap, they are not coextensive. The search also involves extensive non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 12.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Drawings

The Drawings submitted in this application has been accepted by the Examiner for examination purposes only.

Specification

The disclosure is objected to because of the following informalities: Applicants have not provided a figure description for figure 13. Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites "glycosyltransferase" in line 9 with incorrect spelling. Appropriate correction is required.

Claim 3 is objected to because of the following informalities: Claim 3 recites the phrase "bacteria cells". Appropriate correction is required.

Claim 5 is objected to because of the following informalities: Claim 5 recites the phrase "The according to". It appears that applicants intended to recite "the process according to...". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and claims 3-6 depending from claim 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 2 recite the phrase "biological activity of". Recitation of the phrase "biologically active" renders the instant claims vague and indefinite. A biologically active protein may encompass a variety of different biological activities. These include but are not limited to immunological activity, such as acting as an antigen for an antibody; regulatory activity, such as that exhibited by many proteins which control transcription and/or translation of not only their encoding nucleic acids but other nucleic acids as well; or enzymatic activity.

The scope of the above phrase is not clear to the Examiner. Especially in the above case it has been recognized that the ypfP gene product of *B.subtilis* has cell envelope biosynthesis activity and the polypeptide isolated from *S.aureus* has been identified as having methacillin resistance activity in addition to cell envelope biosynthesis activity. A sequence search of SEQID NO:2 and 4 also indicates that the above polypeptide has DNA-binding activity, phosphoribosyltransferase activity, dihydrofolate reductase activity and thymidylate synthase

activity etc. It is not clear to the Examiner as to whether the phrase "biological activity" encompasses all the above activity or is directed specifically to "processive diacylglycerol glycosyltransferase" activity only and nothing else. A perusal of the specification does not indicate a specific definition for "biological activity".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the process of producing glycolipids such as the diacylglycerols (mono, di, tri and tetraglucosyl or the respective glycosyl compounds), glycosylceramides (mono and di-glycosyl or the respective glucosyl compounds), steryl glucosides (mono and di- glucosyl or their respective glycosyl) and glucosylphosphotidylglycerol (mono and di-) does not reasonably provide enablement for a process of producing any or all types of glycolipids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6 are so broad as to encompass the process of making any glycolipid. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glycolipids broadly encompassed by the claims. The specification is limited to teaching use of the above enzyme for producing few glycolipids but provides no guidance with regard to production of all other types of glycolipids using the provided enzyme (for example the complex glycolipids of bacterial cell wall) nor provides a teaching of other enzymes for the synthesis of other glycolipids. Since glycolipids comprise a diverse group of molecules with different glycosyl groups and different lipid acceptor groups and since applicants have not shown that all these types of glycolipids can be produced by the single enzyme provided, one of ordinary skill in the art requires a knowledge of and guidance with regard to methods and reaction conditions required and additional enzymes if any, for producing the diverse group of glycolipid compounds and detailed knowledge of the ways in which the given enzyme can be used for such a process. However, in this case the disclosure is limited to process of producing only few of the glycolipids.

The specification does not support the broad scope of the claims which encompass the process of producing all glycolipids because the specification does not establish: (A) a rational and predictable scheme for process of producing all or any glycolipid using the enzyme provided; and (B) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a process of making any glycolipid. The scope of the claims

must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the use of the enzyme for producing all glycolipids is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enzymes with SEQ ID NO:2 or 4, with a processive diacylglycerol glycosyltransferase (PDG) activity, isolated from either *B.subtilis* or *S.aureus* does not reasonably provide enablement for any PDG from any or all sources. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6 are so broad as to encompass any PDG from any source including recombinants, variants and mutants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of PDGs broadly encompassed by the claims. Since the amino acid sequence of a protein determines its

structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim. The disclosure is limited to the amino acid sequences of only two PDGs.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple sources or to screen for multiple substitutions or multiple modifications, or as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any PDGs because the specification does not establish: (A) a

rational and predictable scheme for isolating and using any PDG from any source; (B) regions of the PDG protein structure which may be modified without effecting its activity; (C) the general tolerance of PDGs to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue in any PDG with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any PDG from any source. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of PDGs having the desired enzymatic characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6 are directed to a process of producing glycolipids using the polypeptide corresponding to the sequence of SEQ ID NO:2 or 4 or other processive diacylglycerol glycosyltransferases. Claims are rejected under this section of 35 USC 112 because the claims are directed to a process of producing any glycolipid using a genus of polypeptides derived from

SEQ ID NO:2 or 4 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 and fragments of SEQ ID NO:2 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 or 4 for the above purpose has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2 or 4, including fragments and variants within the scope of the claimed genus. The genus of polypeptides used in the claims is a large variable genus including peptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses a method using only two species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorokin et al. (SwissProt Database, Accession No. P54166, Oct. 1996), Kunst et al. (PIR Database, Accession No. C69935, Dec 1997), and Price et al. (J. Bacteriol., 1997, Vol. 179(15):4959-4961). Claims 1-3 in this instant application are drawn to a method of producing glycolipids in transgenic cells or organisms wherein the process comprises transferring a polynucleotide with SEQ ID NO:1 encoding a polypeptide with SEQ ID NO:2 having a processive glycosyltransferase activity capable of forming a glycosidic bond between a sugar residue and a lipid-linked substrate, wherein such polynucleotides are obtained from *B.subtilis* or *S.aurues*.

Sorokin et al. and Kunst et al. teach (nucleic acid sequences) and amino acid sequences that are 100% identical to the polypeptide with SEQ ID NO:2 encoded by SEQ ID NO:1. While Kunst et al. identify the polypeptide and the polynucleotide as cell wall synthesis homolog ypfp, Sorokin et al. identify the same polypeptide sequence as a glycosyltransferase. However, both references do not teach that the glycosyltransferase is processive has the capacity to transfer sugar molecules to lipid-linked substrates to synthesize glycolipids.

Price et al. teach the characterization of the ypfp gene product. The reference teaches that the ypfP polypeptide is similar to monogalactosyldiacylglycerol synthase (MGDG) of *Cucumis sativus* and murG of *B.subtilis, E.coli* and *H.influenzae* which encode the enzyme involved in peptidoglycan biosynthesis. Further, by comparing the sequences, the reference teaches that stretches of amino acid sequences among the murG, MGDG and ypfP are functionally similar and that ypfP plays an important role in cell envelope biosynthesis or maintenance. Importantly the reference teaches that MGDG and murG catalyze the formation of a glycosidic bond between a sugar residue and a lipid-linked substrate and that while MDGD

transfers galactose from UDPgalactose to 1,2,-diacylglycerol, murG transfers GlcNAc from UDP-GlcNAc to lipid-linked MurAc-pentapeptide. Thus one of ordinary skill in the art would conclude that ypfP product being so identical to murG and MGDG would also have glycolipid synthesizing activity.

Armed with such a conclusion and also combining the above three references, it would have been obvious to one of ordinary skill in the art to take the sequences provided by Kunst et al. or Sorokin et al. and use it to transform a bacterial or plant cell and express the polypeptide such that those transformed cells would produce glycolipids which can be isolated from the culture supernatant or the cell extract. One of ordinary skill in the art would conclude that the enzyme has processive activity after analyzing the glycolipids formed. One of ordinary skill in the art would have been motivated to do so because of the ease in producing glycolipids in a bacterial cell culture as opposed to the complex methods of chemical synthesis. One of ordinary skill in the art would have a reasonable expectation of success as Price et al. teach the function of the ypfP product and Sorokin et al. or Kunst et al. teach or provide the polypeptide and polynucleotide sequence for the ypfP product and the art is rich in transformation methods that have been used by a number of other inventors.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Steadman, Ph.D.
5/3/02

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